

Anemia Is Common in Heart Failure and Is Associated With Poor Outcomes

Insights From a Cohort of 12 065 Patients With New-Onset Heart Failure

Justin A. Ezekowitz, MBBCh; Finlay A. McAlister, MD, MSc; Paul W. Armstrong, MD

Background—Although previous work has suggested that anemia is associated with an increased mortality in selected patients with congestive heart failure (CHF), little is known about the prevalence and predictors of anemia, or whether anemia is an independent prognostic factor in unselected, community-based patients with CHF.

Methods and Results—We analyzed a population-based cohort of patients with new-onset CHF from a database of patients discharged from 138 acute-care hospitals in Alberta, Canada, between April 1993 and March 2001. Logistic regression, Kaplan-Meier survival analyses, and Cox proportional hazards model were used. Among the 12 065 patients with CHF (median age 78 years), 17% had anemia, 58% of whom had anemia of chronic disease. After adjustment for clinical and demographic variables, patients with anemia were more likely to be older (odds ratio [OR] 1.01 per year) and female (OR 1.2 [95% confidence interval 1.1 to 1.3]) and to have a history of chronic renal insufficiency (OR=3.2 [95% confidence interval 2.8 to 3.6]), or hypertension (OR 1.3 [95% confidence interval 1.2 to 1.5]). Hazard ratios for mortality, adjusting for covariates, were 1.34 (1.24 to 1.46) in anemic patients, and 1.36 (1.23 to 1.50) in those patients with anemia of chronic disease.

Conclusions—In this large cohort of community-dwelling patients with CHF, anemia is common and an independent prognostic factor for mortality. Further research into the mechanisms of anemia in CHF and randomized controlled trials to test whether correction of anemia improves prognosis in CHF are needed. (*Circulation*. 2003;107:223-225.)

Key Words: anemia ■ heart failure ■ epidemiology

Despite remarkable advances in diagnosis and therapy over the past decade, the prognosis of patients with heart failure remains poor. Identification of factors that adversely affect quality of life or survival in heart failure may not only aid in better definition of prognosis but could also potentially provide new opportunities for novel therapeutic strategies in these patients.

Although anemia (and its correction) is a well-recognized comorbidity in a variety of conditions, including myocardial ischemia, its role in heart failure has only recently received attention.¹⁻⁴ Two studies have examined the prevalence and prognosis of anemia in highly selected CHF populations; prevalence was 4% in clinical trial participants (n=6797) with asymptomatic or mild left ventricular dysfunction (relative risk [RR] for death was 1.03 [95% confidence interval (CI) 1.02 to 1.04] for each 1% drop in hematocrit in this sample),¹ whereas 30% of patients (n=1061) followed-up in a specialized clinic for advanced heart failure had anemia (RR 1.13 [95% CI 1.05 to 1.22] for mortality).² In a small population-based cohort (n=633) of Medicare beneficiaries admitted to hospital for CHF, 14% had an admission hemat-

ocrit <30%, and these anemic patients had increased mortality at 1 year (RR 1.60 [95% CI 1.19 to 2.16]) compared with those with a hematocrit ≥40%.³ Little is known about the prevalence or prognostic importance of anemia in a large unselected population of patients with heart failure.

Methods

We examined a population-based cohort of 12 065 patients with new-onset heart failure in Alberta, Canada (total population 3.06 million). We used hospital discharge data to identify all patients hospitalized at least once for a most responsible diagnosis of heart failure (International Classification of Diseases [ICD]-9 code 428.x) between April 1993 and March 2001, and collated their comorbidities. The accuracy of our data acquisition and the use of discharge coding to identify cases and comorbidities have been described elsewhere.^{5,6} To establish a cohort of incident cases, we excluded patients hospitalized for heart failure in the 12 months preceding the index hospitalization, as well as those who died during the index hospitalization.

We linked the study sample to the Alberta Health Care Insurance Registry, which tracks the vital status of all individuals in the province, and followed-up with all patients from the date of their index hospitalization until the date of their death or September 30, 2001, whichever came first. We determined the prevalence of anemia

Received October 23, 2002; revision received December 3, 2002; accepted December 4, 2002.

From the Division of Cardiology (J.A.E., P.W.A.) and the Division of General Internal Medicine (F.A.M.), University of Alberta, Edmonton, Alberta, Canada.

Correspondence to Paul W. Armstrong, MD, 2-51 Medical Sciences Building, University of Alberta, Edmonton, Alberta, Canada T6G 2H7. E-mail paul.armstrong@ualberta.ca

© 2003 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000052622.51963.FC

Clinical Features in 12 065 Heart Failure Patients With Any Anemia, Anemia of Chronic Disease, or No Anemia

Characteristic	Anemia of Chronic		
	Any Anemia (n=2083)	Disease (n=1208)	No Anemia (n=9982)
Age, y	77.3±12*	77.3±11*	76.4±12
Male sex	944 (45)*	570 (47)*	4972 (50)
Diabetes	532 (26)	347 (29)*	2346 (24)
Hypertension	738 (35)*	452 (37)*	2829 (28)
COPD	625 (30)	372 (31)	2879 (28)
Hyperlipidemia	78 (4)	58 (5)	349 (4)
Ischemic heart disease	868 (42)*	540 (45)*	3805 (38)
Cerebrovascular disease	107 (5)	58 (5)	393 (4)
Peripheral vascular disease	200 (10)*	117 (10)*	550 (6)
Atrial fibrillation or flutter	548 (26)	313 (26)	2460 (25)
Malignancy	228 (11)*	131 (11)*	536 (5)
Chronic renal insufficiency	387 (19)*	277 (23)*	674 (7)

Values are presented as mean±SD or n (%). Note that the 1208 patients classified as having anemia of chronic disease represent a subset of the 2083 patients with any anemia. COPD indicates chronic obstructive pulmonary disease.

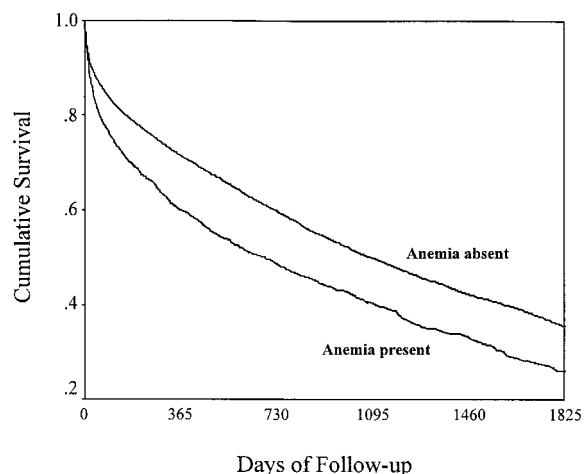
* $P < 0.005$ for comparison with no anemia. Statistical significance adjusted for multiple comparisons using the Bonferroni correction.

at the time of initial diagnosis of heart failure (using ICD-9 codes 280 to 289 to capture "all anemia" and 285.9 to capture "anemia of chronic disease") and examined for differences between patients who did and did not have anemia at baseline (Table). Continuous variables were compared using ANOVA adjusted for multiple comparisons by Tukey's test, and ordinal and dichotomous variables were compared using the χ^2 test. Mortality rates of patients who were anemic when heart failure was diagnosed and those without anemia were compared using the Cox proportional hazards model, controlling for comorbidities and the known prognostic factors in heart failure (listed in the Table). Data for regression analysis is presented as odds or hazard ratio with 95% confidence intervals. In a sensitivity analysis to minimize confounding by unmeasured comorbidities, we examined the associations between anemia and outcomes in the youngest and healthiest subgroup (patients <65 years without documented comorbidities).

Results

The median age of our 12 065 patients was 78 years; 17% had anemia (21% iron deficiency, 8% other deficiency, 13% assorted other identifiable causes, and 58% had anemia of chronic disease). Baseline features are outlined in the Table. On multiple logistic regression analysis, anemia was more common in older patients (odds ratio [OR] 1.01 per year, $P = 0.002$), women (OR 1.2 [1.1 to 1.3]), patients with chronic renal insufficiency (OR 3.2 [2.8 to 3.6]), or hypertensive patients (OR 1.3 [1.2 to 1.5]).

Median follow-up was 573 days (interquartile range 155 to 1224 days), and the 1-year and 5-year mortality rates were 38% and 59% in those with anemia, respectively, compared with 27% and 50% for those without anemia. The survival of patients with anemia was worse even after adjustment for the known prognostic factors and comorbidities in the Table (Figure). Cox proportional hazard ratios for mortality were 1.34 (1.24 to 1.46) in anemic patients, and 1.36 (1.23 to 1.50) in the subset of patients with anemia of chronic disease. As a sensitivity analysis,



Survival of heart failure patients with and without anemia at the time of initial diagnosis of heart failure. These survival curves were generated using Kaplan-Meier methods ($P < 0.0001$ for anemia present versus anemia absent). For results of Cox proportional hazards modeling, please see text.

we restricted this analysis to the youngest and healthiest subgroup ($n = 654$) and found that anemia was even more strongly associated with mortality (OR 2.4 [1.2 to 4.6]).

Discussion

The key novel findings of our study are the demonstration among a large population-based cohort of CHF patients that anemia is common, that it is an independent prognostic factor, and that the majority of heart failure patients with anemia have anemia of chronic disease. There are several possible explanations for our findings. First, reduced hemoglobin may merely be a marker for the epiphenomena of advanced heart failure (such as hemodilution due to volume overload, malnutrition from cardiac cachexia, or renal insufficiency). An earlier study in patients with New York Heart Association class III or IV failure demonstrated, however, that hemoglobin was an important prognostic factor independent of the pulmonary capillary wedge pressure, body mass index, serum albumin, or serum creatinine.² Furthermore, anemia was an independent predictor of mortality independent of serum creatinine in 2 previous studies.^{1,3} Second, because angiotensin-converting enzyme (ACE) inhibitors may inhibit hematopoietic cell proliferation, it is possible that anemia may be a marker for patients receiving higher doses of ACE inhibitors.^{7,8} This seems unlikely, however, as the presence of anemia seems to be independent of ACE inhibitor use (and dosing).^{1,2} Third, although anemia may predispose at-risk patients to myocardial ischemia, the prognostic impact of anemia was independent of a diagnosis of ischemic heart disease in our data. Finally, inflammation, characterized by increases in cytokines such as tumor necrosis factor- α ,⁹ is now thought to be a pathophysiological modulator of heart failure. Hence, we believe it is reasonable to hypothesize that heart failure may cause anemia of chronic disease through cytokine-mediated bone marrow suppression.⁷

As this is an observational study, some potential limitations deserve discussion. The limitations of administrative data-

bases are well known and described elsewhere.⁵ However, previous studies have confirmed the accuracy of our data sources and coding for heart failure.^{5,6} Further, all of our analyses were adjusted for known prognostic factors in heart failure, and we confirmed the robustness of our findings in a sensitivity analysis in the youngest and healthiest subgroup, where unmeasured confounding would presumably be minimized.¹⁰

We believe efforts to better detect anemia in heart failure patients, discern the pathophysiology of, and test new therapies for anemia in heart failure should be a future priority. Indeed, small open-label studies have shown improvements in functional capacity and ejection fraction with correction of anemia using erythropoietin with intravenous iron.^{4,11} There is clearly a need for an appropriately powered randomized trial with meaningful clinical endpoints, such as hospitalizations and mortality, to evaluate the impact of such therapies in anemic heart failure patients.

Acknowledgments

This study was supported in part by a grant-in-aid from the Medical Services Innovation Fund from the Alberta Medical Association and Alberta Health and Wellness. Dr McAlister is a Population Health Investigator of the Alberta Heritage Foundation for Medical Research. J. Ezekowitz is a Canadian Institutes of Health Research Strategic Training Fellow in TORCH (Tomorrow's Research Cardiovascular Health Professionals). No funding agency had input into the design, conduct, analysis or reporting of this study. We thank Nicole Franjic and Wei-Ching Chang for their assistance with data management and statistical support.

References

1. Al Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol*. 2001;38:955–962.
2. Horwich TB, Fonarow GC, Hamilton MA, et al. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol*. 2002;39:1780–1786.
3. McClellan WM, Flanders WD, Langston RD, et al. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. *J Am Soc Nephrol*. 2002;13:1928–1936.
4. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol*. 2000;35:1737–1744.
5. Sin D, McAlister FA. The impact of beta-blockers on morbidity and mortality in a population-based cohort of 11 942 elderly patients with congestive heart failure. *Am J Med*. In press.
6. Goff DC Jr, Pandey DK, Chan FA, et al. Congestive heart failure in the United States: is there more than meets the I (CD code)? The Corpus Christi Heart Project. *Arch Intern Med*. 2000;160:197–202.
7. Iversen PO, Woldbaek PR, Tonnessen T, et al. Decreased hematopoiesis in bone marrow of mice with congestive heart failure. *Am J Physiol Regul Integr Comp Physiol*. 2002;282:R166–R172.
8. Macdougall IC. The role of ACE inhibitors and angiotensin II receptor blockers in the response to epoetin. *Nephrol Dial Transplant*. 1999;14:1836–1841.
9. Levine B, Kalman J, Mayer L, et al. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med*. 1990;323:236–241.
10. Wen SW, Hernandez R, Naylor CD. Pitfalls in nonrandomized outcomes studies: the case of incidental appendectomy with open cholecystectomy. *JAMA*. 1995;274:1687–1691.
11. Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol*. 2001;37:1775–1780.